REMARKS

Applicants have carefully considered the Examiner's Non-Final Office Action, and respectfully request reconsideration of this Application in view of the above Amendment and the following remarks.

(a) Pending in this Application are Claims 1-20 and 36;

(b) Claims 1-20 and 36 are claims the have been selected by the Applicants indicated in the restriction election requirement;

(c) Claims 21-35, 37 and 38 have been withdrawn from further considerations as being drawn to a non-elected invention as indicated in the restriction election requirement;

(d) Claims 1, 7, 11-13, and 18 are amended currently with changes as indicated;

(e) Claims 2, 3, 4, 5, 14, 15, 20, and 36 were amended previously with prior changes not indicated; and

(f) Claims 6, 8, 9, 10, 16, 17, and 19 are the original claims.

Amendments to Claims:

The amended claims find support throughout the specification, including the following sections:

Claim 1, 7, 11-13, and 18	Page 5, lines 24-30; Page 10, lines 7-20; and Page 11, lines 15-40; and Page 12, lines 1-30; Page 13, Lines 1-30; Page 14, lines 1-35; Page 15, lines 1-25; Page 16 lines 13-32; Page 17, lines 10-30; Page 19, lines 10-22 Tables 1-5, and elsewhere throughout the original claims and specification.

I. Rejections Under 35 U.S.C. §112 First Paragraph

The Examiner has rejected Claims 18 under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. The Examiner is of the opinion that there is no support in the original specification for a detection of a combination of lysosomal storage disorders.

Applicants respectfully disagree. Page 19, lines 7-9, of the specification has this to say:

> "The relative levels of the different markers can also sometimes provide an indication that a particular lysosomal storage disorder or subset of disorders is present (see Table 1)."

Applicants have amended the phrase "and combination thereof," from Claim 18 to read "and subset thereof."

II. Rejections Under 35 U.S.C. §112 Second Paragraph

The Examiner has rejected Claims 1-20 and 36 under 35 U.S.C. §112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which the applicant regards a the invention. The Examiner is of the opinion that Claims 1, 7, 11, 12, and 13 are vague.

Rejection of Claim 1: The Examiner has specifically stated that Claim 1 is vague because:

> "Applicant has not indicated which specific lysosomal disorder, nor a specific level of saposin or specific level of increase or specific level of decrease level of saposin indicate the presence of the specific disease."

Applicants have amended Claim 1 to include the limitation of "comparing the first level to a baseline level."

The Court has held:

> "There is nothing vague or confusing about a claim when, in the light of the specification and drawings, the disclosure makes the invention sufficiently clear to enable a mechanic skilled in the involved art to construct and use the claimed subject matter." *The Tillotson Manufarcturin Company v. Textron, Inc.,* 337 F2.D 833, 143 U.S.P.Q 268, 274 (6th Cir. 1964).

Applicants respectfully submit that one of ordinary skill in the art would have been aware at the time of the invention that one common feature of LSDs is the accumulation and storage of materials within lysosomes. It was generally recognized that the accumulation and storage of material in LSD affected individuals results in an increase in the number and the size of lysosomes within a cell from approximately 1% to as much as 50% of total cellular volume. Thus, in non-affected individuals, such materials are typically degraded into degradation products within the lysosome and then transported across the lysosomal membrane.

The specification describes how certain lysosomal proteins (e.g. lysosome-associated membrane proteins ("LAMPs"), saposins, and α–glucosidase) are present at elevated levels or depressed levels in the tissue lysosomes of affected individuals when compared to a control population (persons not having the disease) (See, Page 3, lines 20-34; Page 4, lines 12-34; Page 6, lines 12-22; and Page 7, lines 4-12).

Applicants invention describes a method that utilizes relative levels of these identified proteins biomarkers found in plasma, serum, whole blood, urine, or amniotic fluid samples for an early diagnosis of all LSD's. For example, sensitive immunoquantification assays have been developed to monitor the relative levels of useful biomarkers such as the lysosome-associated membrane proteins ("LAMPs"), saposins, and α–glucosidase when compared to baseline levels. Although the determination of relative levels of saposin alone in an 'at-increased-risk' group will identify LSD affected individuals, the combination of a saposin with a second saposin or a LAMP increase identification of LSD in affected individuals. Therefore, a method to identify and monitor two or more biomarkers simultaneously increases the accuracy of diagnosing a specific LSD as compared to any single assay. Support can be found throughout the specification (e.g. Tables 1-5, Page 5, lines 24-30; Page 10, lines 7-20; and Page 11, lines 15-26), in particular, Pages 12-15 and Tables 1-5 of the specification.

Diagnosing a specific LSD using a single saposin or relative protein profiling levels of several different biomarkers would be difficult without tables indicating which single or combination of biomarkers showed "strong positive" correlations (i.e. at least 80% of subjects with the disorder having a level of marker of at least a 95th percentile of a control population); a "positive" correlation (i.e. at least 40% of subjects with the disorder have a level of marker of at least the 95th percentile in a control population); no correlation; or a negative correlation. See Tables 1-5 and Pages 12-13 of the specification.

In contrast to the Examiner opinion on page 3 of the Office Action that:

> "In line 6, the recitation of "similar or different" is vague and indefinite as to what level of saposin is determined."

The Court has held that:

> "A term is only indefinite if one skilled in the relevant art would not understand what is claimed even when the claim is read in light of the specification. A decision on whether a claim is invalid [for indefiniteness] requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Rhone-Poulenc Agrochime S.A. v. Biagro Western Sales* Inc. 35 U.S.P.Q. 2d 1203, 1205 (Cal. 1994).

Applicants respectfully submit that:

> "...by examining the levels of several or all of the markers shown in a patient and comparing with the correlations shown in Table 1 or similar Table it is possible to classify a patent as having a particular disease or subset of diseases,..." as indicated on Page 13, lines 21-23 of Applicants specification.

Additionally, Page 19 lines 7-23, and Tables 1-5 discuss the saposin levels in the plasma of control and LSD-Affected individuals:

> "To evaluate the suitability of each of the saposins as markers for new born screening for LSD, the levels of saposins A, B, C and D were determined in the plasma samples from 111 control individuals (median age = 7, range =0-66) and 334 LSD affected individuals, representing 28 different disorders (Table 1)."

Applicants submit that the above paragraph and Tables 1-5 also addresses the Examiner concerns that the claims are not clear as to what level of saposin and/or which of the 4 saposin is correlated to each of the 30 lysosomal storage disorders.

Additionally, the Court has held that:

> "The PTO has the burden of giving reason, supported by the record as a whole, why the specification is not enabling, and showing that the disclosure entails undue experimentation would be one way of meeting that burden." *In re Morehouse and Bolton*, 545 F.2d 162, 192 U.S.P.Q. 29, 31, 32 (C.C.P.A. 1976).

Applicants respectfully submit that the Examiner has NOT provided evidence to indicate that one of ordinary skill in the art would consider the terms "similar or different" as vague and indefinite as to the level of saposin determined to have a strong or weak correlation with a

specific LSD. This is especially the case given the detailed analysis Tables 1-5 of the specification.

The Examiner has stated that parts (i) and (ii) Claim 1 are further specifically vague, and has requested Applicants to answer the following question:

> "If the first level is similar to the base line level of the control population of patients unaffected by lysosomal storage disorder, how can the first level be an indicator of the presence or extent of the lysosomal storage disorder?"

Respectfully, Applicants have already given the answer on Page 14 lines 5-15:

> "If the measured level of an analyte does not differ significantly from baseline levels in a control population, the outcome of the diagnostic test is considered negative.....For saposins and Lamp-1, a positive outcome is typically indicated by measured levels in excess of normal levels..... The extent of departure between a measured value and a baseline value in a control population also provides an indicator of the probable accuracy of the diagnosis, and/or of the severity of the disease being suffered by the patient."

The Examiner is also of the opinion Claim 7 is indefinite since it is not clear as to what the measured level that is greater than 95% level in the control population indicates. The Examiner has requested Applicants to answer the following question:

> "Does it [measured level that is greater than 95% level] indicate the presence of the disorder?" [emphasis added]

Applicants respectfully direct the Examiner to amended Claim 7, which now reads as follows:

> 7. The method of claim 4, wherein the ~~measured~~ first level is greater than the $\underline{95^{th}}$ percentile <u>of the baseline</u> level in the control population.

Applicants respectfully disagree with the Examiner's assertion on the clarity of using the term 95^{th} percentile to indicate a measured level in a control population of a diagnostic assay. By definition, "percentile" is a value on a scale of one hundred that indicates the percent of a distribution that is equal to or below it (See Exhibit A). Thus, a percentile measured level of 95 is a measured level equal to or better than 95 percent of the measured levels in the control population. In this field, it is customary to use percentiles to describe the separation of control

and potentially affected groups, as is indicated in the specification on Page 10, lines 15-20; Page 11, 22-25; Page 16 table 2; Page 17, lines 26-31; and elsewhere throughout the specification.

Rejection of Claim 11 and 12: The Examiner maintains that Claims 11 and 12 are vague because they are not clear as to what level of saposin indicates a progression of the disorder. The Examiner is also of the opinion that the claims are not clear as to what level of saposin and/or which of the 4 saposin is correlated to each of the 30 lysosomal storage disorders.

In response, Applicants direct the Examiner's attention to Page 19, lines 7-23, and Tables 1-5, which discuss the saposin levels and clarify which of the 4 saposin proteins are correlated to each of the 28 lysosomal storage disorders.

> "To evaluate the suitability of each of the saposins as markers for new born screening for LSD, the levels of saposins A, B, C and D were determined in the plasma samples from 111 control individuals (median age = 7, range =0-66) and 334 LSD affected individuals, representing 28 different disorders (Table 1)."

Applicants submit that Tables 1-5 are of sufficient detail to ascertain and correlate saposin protein levels to each of the LSD disorders.

Thus, Applicants submit that the claims are precise and definite enough to provide a clear-cut indication of the scope of the claimed subject matter in light of the specification.

Turning now to the merits of the claims, Applicant's invention provides a method of diagnosing or monitoring a lysosomal storage disorder from a sample in a patient by measuring a level of at least a one saposin in a sample of obtained from the patient, wherein the level of saposin is similar or different from a baseline level of saposin determined in a control population of patients that are unaffected by the lysosomal storage disorder. Using the level of one or more saposins from an easily obtainable sample of plasma, serum, whole blood, urine, or amniotic fluid sample as an indicator of presence or extent of the lysosomal storage disorder in a patient is unique.

II. Rejections Under 35 U.S.C. §103(a)

A. Claims 1, 4, 7, 13-15, 17 and 18 stand rejected under 35 U.S.C. §103(a) over the O'Brien '1991 Reference in view of the Sano '1989 Reference.

Applicants submit that each of Claims 1, 4, 7, 13-15, 17, and 18 contains a limitation that distinguishes the samples used for a method of diagnosing or monitoring an LSD. This limitation is: plasma, serum, whole blood, urine, or amniotic fluid. This recited limitation is not disclosed or suggested in the O'Brien '1991 Reference, wherein the only samples mentioned are

brain, liver and spleen. More specifically, measuring the saposin levels from a biopsy or repeated biopsies of a patient's brain, liver, or spleen, as illustrated in the O'Brien '1991 Reference, is not realistic or practical for a non-invasive diagnostic screening method.

The Examiner is of the opinion that because the Sano '1989 reference indicates that saposin are found in human blood and plasma, therefore, it would have been obvious to one of ordinary skill in the art combine the teaching of the O'Brien '1991 Reference and use blood or plasma as a method of detecting an LSD.

The O'Brien '1991 Reference clearly demonstrates that three different tissues contain three different levels saposin proteins. For example, Figure 7, page 307 of the O'Brien '1991 Reference shows a graph of the accumulation and concentration of saposin A, B, C and D in three different tissues (i.e. Brain, Liver, and Spleen) of control patients and patients having different LSD's. More specifically, NO detectable levels of saposin A, B, C, or D were found in the brains and livers of patients having Gaucher disease. In contrast, the patients having Gaucher disease had the highest spleen concentrations of saposin proteins when compared with the spleens from controls or all of the other LSD patients.

Applicants submit that the knowledge of saposin proteins being found in the blood, as indicated in the Sano '1989 reference, is not a critical link that would allow one of ordinary skill in the art to develop a diagnostic assay for an LSD based upon relative levels of saposin proteins in blood or plasma. Because the amount of saposin proteins can be variable in different tissues and in different LSD's conditions (e.g. as indicated in Figure 7 of the O'Brien '1991 Reference), it is unlikely that one of ordinary skill in the art would have been able to "predict" the alternating levels of the saposin proteins in plasma from control and LSD affected individuals, as indicated in Tables 1-2 of the specification.

According to the Manual of Patent Examining Procedure -(MPEP) §2143 there are three requirements for Prima Facie Obviousness:

1) Some suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

2) A reasonable expectation of success; and

3) Prior art reference (or references when combined) must each list or suggest all of the claim limitations.

Thus, the consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not the applicant's

disclosure. In view of the data presented in the O'Brien '1991 Reference indicating that saposin protein levels are variable in different tissues, and the **absence** of data indicating any specific saposin protein levels in plasma from the Sano '1989 Reference, one of ordinary skill in the art COULD NOT have predicted the relative levels of saposin proteins in the blood needed to diagnose or monitor any LSD conditions. At best, this experiment may be "obvious-to-try." However, "obvious-to-try", or "obvious-to-test" or "experiment" is not a proper standard of 35 U.S.C. §103. *In re Goodwin*, 198 U.S.P.Q. 1,3 (C.C.P.A. 1978); *In re Antonie*, 195 U.S.P.Q. 6,8 (C.C.P.A. 1977); *In re Geiger*, 2 U.S.P.Q. 2d 1276, 1278 (Fed. Cir. 1987); *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1532 (Fed. Cir 1988). In fact, the mere need for experimentation to determine parameters needed to make an invention work is an application of the often rejected "obvious-to-try" standard and falls short of the statutory obviousness of 35 U.S.C §103. The inability of an expert to predict that results obtainable with a claimed product suggests non-obviousness, not routine experimentation. *Uniroyal Inc. v. Rudkin-Wiely Corp.*, 5 U.S.P.Q. 2d 1434, 1440 (Fed. Cir. 1988).

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). The O'Brien '1991 Reference, indicates that the level of each of the saposin proteins in brain, liver, and spleen are present at different levels between tissues. The O'Brien '1991 Reference, also indicates that the level of each of the saposin proteins varies depending upon the type of LSD present in each patient. Additionally, the O'Brien '1991 Reference indicates control patients have relatively low levels of saposin proteins in all of the tissues studied. There is **NO** indication or suggestion that accumulation of saposin proteins in blood, plasma, or any other tissue from patients having an LSD would follow a predictable concentration pattern.

The Sano '1989 Reference, **DOES NOT** indicate, suggest, or even mention the levels of saposin proteins from LSD patients. **NEITHER** the suggestion **NOR** an expectation of successfully predicting that various saposin levels in blood or plasma show strong or week correlations (as shown in Tables 1-5 of the Applicants specification) in patients having various LSD conditions cannot be found in the prior art.

Applicants submit that the combining the cited references **DOES NOT** suggest a reasonable expectation of success for diagnosing or monitoring a LSD using blood or plasma from a patient.

Thus, Claims 1, 4, 7, 13-15, 17 and 18 cannot be considered to be "obvious" over the O'Brien '1991 Reference in view of the Sona '1989 Reference under U.S.C. 35 §103(a).

B. Claims 5, 6, 9-12, 19, 20, and 36 stand rejected under 35 U.S.C. §103(a) over the O'Brien '1991 Reference in view of the Sano '1989 Reference, in further view of the U.S. Patent No.: 6,376,236 issued to Dubensky ("the '236 Patent").

The Examiner is of the opinion that the '236 Patent teaches that patients can undergo responsive treatments for lysosomal disorders and when combined together with the O'Brien '1991 Reference and the Sano '1989 Reference, and it would have been obvious to monitor LSD's.

As discussed above, the combination of both the O'Brien '1991 Reference and the Sano '1989 Reference falls short of rendering the present invention as bein obvious.

Applicants further submit that the '236 Patent teaches a recombinant alphavirus particle. Although the '236 Patent mentions that a specific aplphavirus may help with the treatment of Gaucher's disease, the term *"saposin"* is not even used throughout the 141 page document. Additionally, there is **NO** mention of utilizing or correlating blood or plasma saposin proteins to diagnose or monitor an LSD.

The courts have held that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Applicants submit that that the combined O'Brien '1991 Reference and Sano '1989 reference **DO NOT** suggest a reasonable expectation of success for diagnosing or monitoring a LSD using blood or plasma from a patient, as described above. Applicants submit that data of saposin levels obtained with brain, liver and spleen CANNOT be extrapolated to blood. Additionally, the '236 Patent does not bridge this gap by disclosing a recombinant alphavirus particle that is used to treat one specific LSD (i.e. Gaucher Disease). Furthermore, since the '236 Patent does not even mention the terms saposin, blood or plasma in the context of a diagnostic assay one of ordinary skill in the art **COULD NOT** be motivated to combine the references to obtain the Applicants invention as described in Claims 5, 6, 9-12, 19, 20, and 36.

Thus, Claims 5, 6, 9-12, 19, 20, and 36 cannot be considered to be "obvious" over the O'Brien '1991 Reference in view of the Sona '1989 Reference, in further view of the '236 Patent under U.S.C. 35 §103(a).

C. Claim 16 stand rejected under 35 U.S.C. §103(a) over the O'Brien '1991 Reference in view of the Sano '1989 Reference in further view of the Stastny '1992 Reference.

The Examiner is of the opinion that the O'Brien '1991 Reference and the Sano '1989 Reference discloses the invention substantially as claimed, except for the antibody being a monoclonal antibody. The Examiner is also of the opinion that since the Stanstny '1992 Reference discloses a monoclonal antibody that reacts with saposin C, it would have been obvious to use this monoclonal antibody in the method taught by O'Brien '1991 in view of Sano in order to detect the level of saposin C.

As discussed above, in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The rejection of Claim 16 is respectfully traversed for the reasons listed above for the O'Brien '1991 Reference and the Sano '1989 Reference. Applicants submit that results obtained with brain, liver and spleen CANNOT be extrapolated to blood. Additionally, the Stastny '1992 Reference DOES NOT bridge this gap by disclosing a monoclonal antibody with a high specificity to saposin C.

Applicants submit that the combining references the O'Brien '1991 Reference, the Sano '1989 Reference, and the Stastny '1992 Reference **DOES NOT** suggest a reasonable expectation of success for diagnosing or monitoring a LSD using blood or plasma from a patient, as described above. Thus, Claim 16 cannot be considered to be "obvious" under U.S.C. 35 §103(a).

CONCLUSION

Applicants respectfully submit that, in light of the foregoing Amendments and comments, Claims 1-20 and 36 are all in condition for allowance. A Notice of Allowance is therefore requested for all claims. If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,

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